Claim 45, last line, delete "m" and insert --μm--.

IN THE ABSTRACT:

note: not attached

The Examiner objected to the abstract of the disclosure because the abstract was more than one paragraph. Accordingly, Applicants submit herewith a new abstract, attached hereto.

REMARKS

Claims 19-32, 33, 34 and 36-45 are all the claims pending in the application. The amendments to the claims are editorial in nature and are supported by the disclosure and are as filed. No issues of new matter arise. Accordingly, entry is respectfully requested.

Claim Rejections Under 35 U.S.C. §102

The Examiner has rejected claims 19-23, 26, 28-32 and 38-44 under 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Suzuki et al.

According to the Examiner, Suzuki et al. teach the product of a composition for nasal administration wherein the drug is dispersed on or in the water-absorbing and water-insoluble base and optionally mixed with a water-absorbing and water-soluble base. More specifically, in such a powdery composition according to the Examiner, at least 90% of the particles of the powdery composition have a diameter of 10-250 μm. A polypeptide having a molecular weight

1,000 to 30,000 is exemplified as the drug and such is present in an amount of 1 to 50 wt% of a water-absorbing and water-soluble (gel-forming) base. (abstract; col. 5, lines 10-25; col. 5, lines 53-65; col. 2, line 64 to col. 3, line 25)

The Examiner takes the position that no weight is given to the process by which the product is obtained because Applicants claim a product. Accordingly, the Examiner states that the claims are anticipated by the prior art which teaches the powdery composition. Alternatively, the Examiner also stated that it would have been obvious to one skilled in the art to mix the drug with the water-absorbing and water-insoluble base in order to have the drug dispersed on or in that base and add a water-absorbing and water-soluble base with the reasonable expectation of obtaining a composition that is efficiently absorbed through the nasal mucosa with a sustained release effect.

Applicants would like to bring the Examiner's attention to an important feature of the instant invention, that is, the effect of the "content of the water-soluble and gel-forming base material and water-absorbing and water-insoluble base material".

According to the disclosure in the specification, the present pharmaceutical composition in Examples 1 to 4 shows a higher absorption that Comparative Examples (C.Exs.) 1-5 in Table 1 on page 16. Examples 5 to 8 also show higher absorption than C.Exs. 6-10 on Table 2 on page 17.

The effect can be better explained when calculating the area under the concentration time curve (AUC; pg x min/mL) on the basis of the numerical values shown in Table 1 and 2. These AUCs and their enhancing ratio are shown in Table A. Table A shows the importance of the content of the water-soluble and gel-forming base material to the total of the base materials. In Table A below, when the content is within the present range of 5-40%, the present compositions show a better enhancing ratio compared to the compositions wherein the water-soluble and gel-forming base material were used alone, C.Ex. 1 or C.Ex. 6. Exs. 1 to 4 or Exs. 5 to 8 show more than 1.2 times higher AUC than C.Ex. 1 or C.Ex. 6. The AUC of Beclomethasone Dipropionate i.v. injection may be around 12,000 pg x min/mL. Accordingly, bioavailability (BA; % of "AUC nasal" against "AUC i.v. injection") of C.Ex. 1 appears to be near 50%, and therefore increasing AUC at 1.2 times the present composition Ex. 1 produces 60% of BA.

This enhancement is of pharmaceutical significance.

Table A

	% of HPC	5	20	30	40	0	50	60	80	100
Beclomethasone Dipropionate		Ex.1	Ex.2	Ex.3	Ex.4	C.Ex.1	C.Ex.2	C.Ex.3	C.Ex.4	C.Ex.5
	AUC	8025	9000	10275	11325	6525	6900	5925	2062.5	1725
	Enhancing ratio	1.23	1.38	1.57	1.74	1.00	1.06	0.91	0.32	0.26
Metoclopramide		Ex.5	Ex.6	Ex.7	Ex.8	C.Ex.6	C.Ex.7	C.Ex.8	C.Ex.9	C.Ex.10
	AUC	6150	7425	13350	12150	4500	2925	2625	2250	975
	Enhancing ratio	1.37	1.65	2.97	2.7	1.00	0.65	0.58	0.50	0.22

AUC is shown as pg x min/mL
Enhancing ratio was calculated by dividing each AUC value by the AUC value of C.Ex. 1 and C.Ex.6

As to a preferred embodiment, the effect of "unevenly" produced by the method set forth in claims 20-23, here "unevenly" means the state in which a drug is dispersed more on/in the water absorbing and water-insoluble base material. This "uneven" dispersion provides a high absorption of drugs.

In more detail, attention is directed to Exs. 73 and 76. In these examples, a method of mixing drugs with the water-absorbing and water-insoluble base material beforehand is used to produce the dispersion of drugs "unevenly". Ex. 73 and Ex. 76 show almost twice as high an AUC as C.Ex. 66 and C.Ex. 68 (See Table B below). These higher AUCs achieved by these Exs. 73 and 76 are superior to C.Exs. 66 and 68 and this pharmaceutically significant.

Further in Exs. 70 and 74, a method of mixing drugs with the water-absorbing and water-insoluble base material under freeze-dried conditions is used to produce the dispersion "unevenly" of drugs. Table B also shows that an AUC almost two times higher was attained by invention examples compared to C.Ex. 64 and C.Ex. 66.

In summary, these results in Table B below demonstrate that the embodiments of the present composition having the feature of dispersion "unevenly" of drugs, such as "Carboxyfluorescein" and Fluorescein" as examples of low molecular weight drugs and such as "Salmon calcitonin" as an example of peptides, results in a high absorption of drugs. (compared to the prior art)

Table B

Composition Effect	Drug	Example No.	AUC	Enhancing ratio
Claim 20	Carboxyfluorescein	Ex. 73	705	2.32
		C.Ex. 66	304.5	1.00
	Fluorescein	Ex. 76	735	1.94
		C.Ex. 68	378.75	1.00
Claim 21	Salmon calcitonin	Ex. 70	10162.5	3.30
		C.Ex. 64	3075	1.00
	Carboxyfluorescein	Ex. 74	522	1.71
		C.Ex. 66	304.5	1.00
Claim 22	Fluorescein	Ex. 77	987	2.61
		Ex. 68	378.75	1.00
Claim 23	Salmon calcitonin	Ex. 61	7912.5	4.40
		Ex. 62	8662.5	4.81
		Ex. 63	9262.5	5.15
		C.Ex. 54	1800	1.00

Enhancing ratio was calculated by dividing each AUC value by the AUC value of each C.Ex.

Further, as the Examiner pointed out, Suzuki et al. suggests a powdery composition for nasal administration that contains a polypeptide and a water-absorbing and water-insoluble base,

and a water-absorbing and gel-forming base material in an amount of 1 to 50 wt% (see col. 5, lines 10-25 of Suzuki et al.)

Additionally, Suzuki et al. suggest that in a case where a water-absorbing and gel-forming base material is to be used jointly with the water-absorbing and water-insoluble base material, the final product of the pharmaceutical composition has a much more sustained release effect. (see col. 5, lines 8-9 of Suzuki et al.)

In the final analysis, however, Suzuki et al. only teach the sustained release effect by adding a water-absorbing and gel-forming base material.

"Unevenly" is a crucial aspect of this embodiment. A composition in which the drug is distributed "unevenly" in/on the water-absorbing and water-insoluble base material is as claimed. The Examiner's attention is directed to Ex. 74 and C.Ex. 67 in the specification again.

In the composition of Ex. 74, the drug is distributed "unevenly" in/on the water-absorbing and water-insoluble base material (see Page 35, lines 25 to 33); and in the composition of C.Ex. 67, the drug is distributed "unevenly" in/on the water-absorbing and gel-forming base material (see Page 35, line 37, to Page 36, line 7).

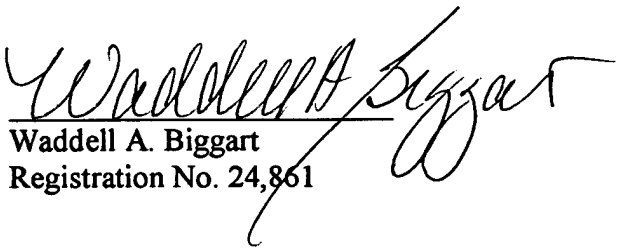
Ex. 74 and C.Ex. 67 show that a composition in which the drug is distributed "unevenly" in/on the water-absorbing and water-insoluble base material significantly attained a higher absorption than a composition of which the drug is distributed "unevenly" in/on the water-absorbing and gel forming base material.

It is to be noted that "unevenly" is not disclosed by Suzuki et al. This point is clarified by the statement in col. 6, lines 38 to 53 of Suzuki et al. in which Suzuki et al. state that the composition is composed of drug which is distributed evenly, not "unevenly", or the composition is composed of drug which is distributed "unevenly" in/on the water-soluble and gel-forming base material, not the water-absorbing and water-insoluble base material. The later composition (underlined above) was manufactured by almost the same method as C.Ex. 67 in the specification and attained a good, sustained plasma profile. However, it is not obvious that the fact of "unevenly" distribution of drugs to the water-absorbing and water-insoluble base material would produce such a high maximum plasma concentration claimed in the instant invention.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such action is hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned at the telephone number listed below.

Applicant hereby petitions for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,



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Date: June 23, 1999